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Chronic fatigue syndrome: its relevance to post-infectious neurological disease

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Chronic fatigue syndrome (CFS) is a debilitating illness of unknown etiology characterized by extreme prolonged unexplained fatigue and a constellation of symptoms often including cognitive and sleep disorders, severe headaches, and muscle and joint pains. Recent studies emphasize the central role of the brain in pathogenesis, and central nervous system symptoms are among the most disabling features. CFS can be acute or gradual in onset and may be precipitated by infection or reveal no obvious precipitating factor. There is no specific diagnostic test or treatment. Current data suggest a heterogeneity to CFS that requires careful description of study groups and analysis of subpopulations when feasible. Although variabilities in the clinical presentation of CFS present major difficulties for analytic studies, a growing body of data showing neuroimmunological abnormalities in CFS suggest that neuroepidemiological studies may yield critical insights into the pathogenesis of this disorder.

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Introduction

Chronic fatigue syndrome (CFS) is a recently defined illness (Holmes et al. 1988, Fukuda et al. 1994) that has become the subject of intense medical scrutiny in the past decade. Although it is a heterogenous disorder and may consist of more than one disease process, the prototype clinical picture is that of severe prolonged fatigue and cognitive dysfunction usually following an infectious disease-like illness. Attention to CFS was catalysed by three reports of chronic Epstein-Barr virus (EBV) infection (Tobi et al. 1982, Jones et al. 1985, Straus et al. 1985) followed by a reported outbreak of a fatigueing illness in northern Nevada/California (Holmes et al. 1987, Buchwald et al. 1992, Levine et al. 1992), where patients exhibited many of the same symptoms previously designated as "chronic EBV infection". The investigation of the northern Nevada/California cluster by the Centers for Disease Control and Prevention (CDC) (Holmes et al. 1987) was followed by a meeting to develop a case definition for this intriguing disorder (Holmes et al. 1988). In addition to the reported clustering of cases of severe unexplained fatigue, the finding of elevated antibody titers to EBV, human herpesvirus-6 (HHV-6) and other viruses suggested that there was an etiological infectious disease agent. It now appears that CFS can be triggered by a number of factors, non-infectious as well as infectious agents, and that it sometimes occurs without any clearly identified trigger. Because debilitating fatigue and cognitive dysfunction can also be found in other neurological disorders of known or suspected infectious origin, such as post-polio syndrome and multiple sclerosis (MS), it may be useful to consider CFS in the context of these other disorders in order better to understand its pathogenesis.

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Historical perspective

CFS was first defined by a panel convened by the CDC (Holmes et al. 1988), but it is clearly not a new disorder. The history of CFS has been discussed elsewhere (Wessley 1995, Demitrack and Abbey 1996), yet much of the interpretation of early reports is speculative and subject to considerable criticism. For example, some historians consider "Soldier's heart" or Da Costa syndrome (Da Costa 1871) an example of CFS, but emphasis on cardiac arrhythmias and the absence of many of the signs and symptoms currently associated with CFS make this association conjectural. Similarly, Florence Nightingale has been cited as having CFS upon her return from the Crimean War, and the early reports suggesting a variety of diagnoses including neurasthenia and stress-induced neurosis (Young 1995) do not exclude the possibility that she did have CFS. But in the absence of the type of medical evaluation now required to rule out other medical or psychiatric disorders, the designation of her case as CFS is inconclusive.

One of the more fascinating aspects of CFS is its association with clusters, e.g. "epidemic neuromyasthenia" (EN) which has been closely intertwined with the history of CFS (Henderson and Shelokov 1957a,b). The first description of a cluster of cases subsequently associated with EN was by Gilliam (1938), who described an outbreak of "atypical poliomyelitis" in 1934. In this cluster, which occurred during the midst of a polio epidemic, an abrupt onset, pain (often joint pain and muscle tenderness), and headache were the primary clinical features, and while there were many similarities to polio, the symptoms waxed and waned and many patients recovered completely.

As case definition is a critical issue in evaluating individuals with various disorders, the same can be said in evaluating clusters of cases. The case definition used for EN by Henderson and Shelokov was remarkably similar to that subsequently developed for CFS, namely:

"The cases have shared the features of a protean symptomatology, including fatigue, headache, alterations in emotional status, aching muscular pain, paresis and paresthesiae. Regarding the severity of illnesses, few significant and consistent physical findings and abnormal laboratory determinations have been noted. The courses of the patients have been unaccountably prolonged and debilitating and marked by frequent exacerbations. Cases have been confined principally to young and middle-aged adults: females have been more frequently and severely afflicted. Although most of the outbreaks have involved the general community, the most notably susceptible have been nurses and physicians. Intensive efforts to characterize these illnesses, etiologically and pathologically, have met with little success" (Henderson and Shelokov 1957a).

It should be emphasized that EN and CFS are not synonymous, however, but that CFS may occur as one outcome of EN. Occasional cases clearly meeting the current case definition of CFS have been documented in outbreaks reported from Punta Gorda, Florida (Poskanzer et al. 1957), West Otago, New Zealand (Levine et al. 1997), and northern Nevada/California (Levine et al. 1992). It is apparent that the cases of CFS occurring in clusters, as with sporadic cases, may have similar clinical features in spite of the apparent diversity of precipitating infectious diseases, such as upper respiratory infections and gastroenteritis. In outbreaks where case definitions were developed in order to investigate the extent of the problem and the potential route of transmission of the putative etiological agent (Poskanzer et al. 1957, Poore et al. 1984), cases of CFS appeared to be in the minority. In one follow-up study as many as 10 out of 21 (48%) traced individuals in a 1986 New Zealand cluster appeared to meet the current CFS case definition (Levine et al. 1997). Clusters continue to provide important opportunities to investigate risk factors for CFS in those who develop the full symptom complex versus those who develop only transient symptoms. In addition to clusters apparently associated with infection, cases of CFS also have been associated with "sick building syndrome", which could involve exposure to toxic chemicals as well as infectious agents (Chester and Levine 1994, 1997), and Persian Gulf-related illnesses, also called "Gulf War Syndrome", in which CFS is at least one manifestation (Revell 1995, Levine 1996).

Epidemiology

Prevalence and case definition

Attempts to investigate the prevalence of CFS have been hampered by continuing changes in the case definition. Both of the case definitions developed by panels convened by the CDC (Holmes et al. 1988, Fukuda et al. 1994) are largely based on clinical impressions and anecdotal interpretations rather than empirical data and are thus considered temporary working definitions. The case definitions, which were developed for research purposes and have major drawbacks for clinical applications, have not been universally accepted (Poser 1995, Komaroff et al. 1996), but continue to be the standard by which all evaluations are measured. The case definitions will probably be revised as improved methods for

documentating the salient clinical abnormalities are forthcoming. Of major benefit would be the discovery of a confirmatory laboratory abnormality, since none of the defects described to date are sufficiently robust or specific.

The importance of case definition in epidemiological studies cannot be stressed enough, and the problem of finding an acceptable case definition has plagued studies of CFS. Initial studies based on the 1988 case definition have resulted in a wide estimate of prevalence of cases, but two studies using a health maintenance organization (Buchwald et al. 1995) and three communities in Chicago (Jason et al. 1995) have reported a prevalence of approximately 200 in every 100,000, suggesting that about 500,000 persons in the US have CFS according to the 1988 criteria of Holmes et al. These studies have a significant advantage over the earlier CDC reports in that the CDC (Gunn et al. 1993, Reyes et al. 1997) attempted a prevalence study that rigidly adhered to the first case definition but, as with an Australian study (Lloyd et al. 1990), suffered from a reliance on physician referral. Given the unwillingness or inability of many physicians to diagnose CFS, such physician referral-based studies may significantly underestimate CFS prevalence.

The recently modified case definition of CFS (Fukuda et al. 1994) has simplified the criteria for diagnosis compared to the earlier one (Holmes et al. 1988), primarily by requiring only four associated symptoms rather than the eight symptoms or physical findings of the first case definition. This change brought about an apparent increase in estimated prevalence. In a direct comparison of the two case definitions in another CDC study (Shefer et al. 1997), more than twice as many persons now meet the diagnostic criteria for CFS than with the original case definition. However, an important weakness of this latter report is the absence of medical evaluation of patients, thus leading to the term "CFS-like". Since the current CDC case definition (Fukuda et al. 1994) emphasizes that medical evaluation is required for the diagnosis of CFS, it is important for investigators not only to specify what case definition has been used for their studies but also to describe the precise evaluation used in excluding other medical or psychiatric conditions associated with fatigue.

The most recent change in surveillance studies was motivated in part by a desire to reduce the expense of prevalence studies. Because of the wide variation in methodology in the seven largest studies to date, a substantial difference in reported prevalence rates, ranging from 2 in 100,000 to 2300 in 100,000 (Levine 1997), is unsurprising. More important perhaps is increasing awareness that patients who fulfil the most recent CDC case definition of CFS (i.e. "full-blown" CFS) may represent only "the tip of the iceberg". Clearly, a spectrum of unexplained fatiguing illness has been observed including patients who do not fulfil the criteria for a diagnosis of CFS, and such patients have been classified as having "prolonged fatigue" or "idiopathic chronic fatigue" (ICF) (Fukuda et al. 1994). These designations appear to be somewhat arbitrary, although it is appropriate for research purposes to distinguish them from patients with CFS. One approach that might be useful in clinical and epidemiological studies is the grading of cases in regard to severity or degree of certainty rather than an arbitrary yes–no classification based on the presence or absence of symptoms. Such an approach has been used in adult T-cell leukemia lymphoma (Levine et al. 1994), in which different case classifications were used in different centers. A grading scheme proposed in Atlanta at the meeting held by CDC regarding the revision of the 1988 case definition was discussed and the resulting modified schema is shown in Table 1.

Table 1 Proposed case classification for chronic fatigue syndrome*

Clinical/routine laboratory	
Acute onset with infection	+1
No previous psychiatric disorder	+1
Cognitive disorder	+1
Severe new headache	+1
Arthralgias/myalgias	+1
Research criteria	
Immunological abnormalities	+1
Low cortisol levels	+1
Exclusion criteria	
Alternative diagnosis	
	Rating
	Classic = 7
	Probable = 5–6
	Possible = 3–4
	Inconsistent = 0–2

* At least six months of unexplained fatigue required.

Patterns of illness

In providing the latest case definition of CFS, Fukuda et al. (1994) noted the importance of distinguishing clinical subgroups. For example, patients who have a history of depression antedating the onset of CFS symptoms are not excluded from the diagnosis of CFS. However, for research purposes such patients should be analysed separately. Several groupings have been suggested, the most common one being the separation of cases with acute onset vs. those with gradual onset. The validity of such separation is supported by several studies in which immunological, cognitive, and psychological patterns have

Table 2 Categorization of outbreaks of epidemic neuromyasthenia according to neurological features (adapted from Briggs and Levine 1994)

	Main features	Representative clusters
Level I (Minimal neurological involvement)	Virtual absence of neurological signs Occasional paresthesiae, subjective weakness Includes depression, non-specific changes in affect	London 1970–71 (Dillon et al. 1974) West Otago, New Zealand 1982–83 (Poore et al. 1984)
Level II (Moderate neurological involvement)	Cutaneous sensory changes. Prominent neuropsychological changes including memory loss, difficulty concentrating, mood changes, depression, problems with word finding	Florida 1956 (Poskanzer et al. 1957, Roueché 1965) New York 1961–62 (Albrecht et al. 1964); New York 1984–87 (Bell et al. 1991); Nevada 1984–87 (Holmes et al. 1987, Daugherty et al. 1991, Levine et al. 1992, Buchwald et al. 1992)
Level III (Severe motor neurological involvement)	Severe extensive paresis, twitching, fasciculation usually without hypotonia, hyporeflexia, muscle atrophy (except Iceland outbreak), cutaneous sensory changes, neuropsychological changes	California 1934 (Gilliam 1938); Akureyri, Iceland 1948–49 (Sigurdsson et al. 1950, Sigurdsson and Gudmundsson 1956) New York 1950 (White et al. 1954); Maryland 1953 (Shelokov et al. 1951)
Level IV (Severe diffuse neurological involvement)	Signs and symptoms of Level III plus mixed upper and lower motor neuron signs, cranial nerve signs, abnormal volitional muscle movements	London 1955 (The Medical Staff of the Royal Free Hospital 1957) Durban, South Africa 1955 (Hill et al. 1959)

been shown to vary according to the type of onset of CFS (DeLuca et al. 1997a, Mawle 1997). Mawle noted that patients with an acute onset had an increased percentage of CD8 T cells expressing CD46 (suppressor T-cell subset), an increased production of IL-2 in response to mitogen stimulation, and an increased proliferation response to candida antigen. In contrast, patients with a gradual onset did not show these changes but did have diminished IL-1B production in response to mitogen and had a lower percentage of CD56 (NK) cells expressing CD2 (T-cell marker). DeLuca et al. studied cognitive function in patients with concomitant Axis I disorders as compared to those without, and noted that the cognitive disfunction, particularly in immediate recall, delayed recall, and backward digit span, was most impaired in those without the concomitant psychological problems (DeLuca et al. 1997b).

Similar considerations should be given to clusters or outbreaks of CFS associated with infections, since different precipitating agents may cause different patterns of disease (Levine 1994). In a study emphasizing neurological manifestations of EN (Briggs and Levine 1994) we showed four distinct neurological patterns in the reports of EN, based on the degree and type of neurological involvement (Table 2). In the reports of clusters the overall pattern of signs and symptoms suggests that different agents were responsible for the different outbreaks. Each cluster had a wide range of manifestations and the categorization of clusters was based on the predominant reported manifestations. In the fatigueing illness in northern Nevada/California in the mid-1980s (Holmes et al. 1987, Daugherty et al. 1991, Buchwald et al. 1992, Levine et al. 1992), for example, the description of a "classic case" consisted of four features: (1) severe prolonged debilitating fatigue, (2) acute onset, (3) severe pain (headache or muscle and joint pains, and (4) severe cognitive disorder (Levine et al. 1992). While most patients did not have manifestations that were consistent with CFS, one patient seen by several physicians had severe transient motor involvement (he was a high school athlete with severe leg weakness requiring crutches, a condition that had completely resolved at a three-year follow-up examination). The marked cognitive involvement with no objective peripheral neurological signs in most patients characterizes this type of outbreak, which we designated as Level II and which resembles the well-documented cluster in Punta Gorda, Florida (Poskanzer et al. 1957) that was investigated by the CDC and led to the designation EN (Henderson and Shelokov 1959a, b).

Reports of clusters of EN have been described periodically over the past six decades, beginning with the first well-documented outbreak of EN reported by Gilliam (1938). Gilliam described a cluster of cases considered as atypical poliomyelitis; similar outbreaks (labeled Level III in our study) were noted in Iceland in 1948–49 (Sigurdsson et al. 1950) and in New York in 1950 (White and Burtch 1954). These clusters may have been caused by a poliovirus variant, since they occurred concurrently with outbreaks of poliomyelitis, and patients demonstrated marked

peripheral neurological findings that have not been characteristic of outbreaks of EN since 1954, when poliovirus vaccination was initiated.

The pattern of EN with few, if any, peripheral signs of neurological disorder, labeled as Level I in our study, is characterized by a cognitive disorder, one of the primary and most disabling features of CFS. This pattern was most prominent in the northern Nevada/California cluster, and was a cardinal feature in our case definition (Levine et al. 1992). Neurocognitive abnormalities were first emphasized, however, in the evaluation of the Punta Gorda cluster in 1957, where the importance of this finding was dramatically described by Roueché (1965) in his detailed expansion of the scientific report by Poskanzer et al. (1957).

"Sick building syndrome" (SBS) has clearly been associated with fatigue but all of the symptoms usually resolve shortly after the patient leaves the area involved (Chester and Levine 1997). SBS has considerable overlap with EN inasmuch as environmental factors appear to make a group of persons in a specific location experience symptoms from exposure to putative infectious or toxic agents. The observation of possible clusters offers the opportunity to identify risk factors for illness by comparing those with symptoms and those without. The importance of a closed-in environment as a possible contributor to CFS/SBS was brought to our attention during the outbreak in northern Nevada/California (Levine et al. 1992), when we noted that a group of teachers in Truckee, California, sharing the same room for preparing and grading examinations all developed CFS with the exception of one teacher, who took his work to the lake. The teachers were aware of an odor from the photocopying machine, and the building was constructed with the features usually associated with SBS (Chester and Levine 1994) including windows that did not open.

The most recent cluster of cases under intensive scrutiny is that developing in some military personnel following return from the Persian Gulf (Revell 1995, Levine 1996). There has been considerable controversy as to whether there is in fact a specific "Gulf War Syndrome" (Levine 1996). Investigations so far have explored the role of noxious agents and the relationship of this syndrome to post-traumatic stress disorder. It also has been postulated that a combination of factors may be necessary for development of this syndrome, e.g. vaccines or infectious agents, neurotoxins, and psychological stress.

Risk factors

The risk factors for CFS have been difficult to determine and the varying reports clearly reflect the differences in the populations evaluated. For example, one of the most consistently reported risk factors has been female gender, with a F:M ratio of 3:1 being reported from most referral centers. However, in an Australian study that may not have been subject to referral bias, an equal female to male ratio was observed (Lloyd et al. 1990). Of interest is the apparent relationship to severity of symptoms and attention to the case definition; in a recent study of a cluster in West Otago, New Zealand, we noted that the M:F ratio in case-defined CFS was 7:1 whereas those with the criteria of ICF, a less debilitating disorder, had a ratio of 3:8 (Levine et al. 1997).

The early suggestions of the prototypical patient as a young white woman in the upper socioeconomic class has now been shown to be a result of referral patterns. CFS has also been well documented in various racial/ethnic (Aoki et al. 1993, Kuratsune et al. 1994, Shefer et al. 1997) and socioeconomic groups (Lloyd et al. 1990, Levine et al. 1992, 1997). Although the peak age at onset appears to be 20–40 years, CFS has been documented in children and the elderly.

An association has been reported for CFS with stressful life events as well as infections (Salit 1997) and in one recent case control study, MacDonald et al. (1996) showed that regular physical exercise was associated with the onset of CFS, a striking finding since several cases occurring in the Lake Tahoe area involved athletes.

Prognosis

The reported outcome of patients suffering from CFS has not been encouraging, but this may be due to the concentration of reports from research and tertiary care centers who see patients with more severe and refractory symptoms. (For a review of studies, see Levine 1997.) Although most published series list poor outcomes, many people seem to recover from CFS, some completely (i.e. return to baseline functioning) and some partially, through coping or modifying their lifestyles (Vercoulen et al. 1996). Current evidence suggests that patients with an acute onset of disease improve faster than those with a gradual onset. Also, patients identified as part of a cluster appear to have a better prognosis than sporadic cases (Levine et al. 1992, 1997). General theories have been advocated for these differences, but earlier medical intervention and support are probably important factors.

Pathogenesis

While the etiology and pathogenesis of CFS remain unknown, studies carried out over the past decade

indicate that many patients have abnormalities of the brain-immune axis. Of potential relevance to understanding these abnormalities has been a substantial body of evidence emerging from the field of psychoneuroimmunology demonstrating that there are bidirectional interactions between the CNS and the immune system (Weigent and Blalock 1995, Chrousos 1995). On the one hand, disturbances of the CNS can affect the immune system, and on the other hand, activation of the immune system can alter CNS function. In particular, "stress", both of a psychological and physical nature, seems to affect a variety of responses of the immune system (Glaser and Kiecolt-Glaser 1992, in press). Psychological stressors that have been best studied are academic pressures, loss of loved ones, and caring for parents with chronic illness, such as Alzheimer's disease. Physical stressors include several infectious disease and toxic agents.

The hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) appear to be the critical neuroendocrine systems that mediate the effects of stress on the immune system, and derangements of both of these neuroendocrine systems have been reported in studies of CFS patients. Since the original report by Demitrack et al. (1991) describing low cortisol levels in a series of patients studied at the National Institutes of Health (NIH), evidence has been accumulating that abnormality of the HPA axis plays an important role in the pathophysiology of CFS (Dinan et al. 1997). Abnormalities similar to those found in CFS have been reported in post-polio syndrome (Bruno et al. 1996), and both disorders have been shown to have similar brain lesions by magnetic resonance imaging (MRI) (Natelson et al. 1993). Inconsistent abnormalities on MRI and other brain imaging techniques, however, preclude any diagnostic value of these procedures (Mayberg 1996).

Evidence pointing to a pathogenic role of the autonomic nervous system (ANS) has been provided recently by studies from Johns Hopkins University (Bou-Holaigah et al. 1995a, b). In these studies, CFS patients have been found to have an inappropriate fall in blood pressure upon assuming an upright posture. The basis for this pathological response has been postulated as due to ANS dysfunction (neurally mediated hypotension). Although the primary site of this ANS defect has not been established, it is possible that areas within the brain stem where ANS control originates are involved.

A variety of immunological abnormalities have been reported in CFS (Chao et al. 1991, Gupta and Vayuvegula 1991, Landay et al. 1991, Lloyd et al. 1993, Straus et al. 1993, Barker et al. 1994, Patarca et al. 1994, Tirelli et al. 1994, Bates et al. 1995, Levine et al. 1996, Swanink et al. 1996, Bennett et al. 1997), although these abnormalities have often been seen inconsistently in different laboratories and have been of modest severity, with considerable overlap between CFS and control groups. The studies demonstrating abnormalities of the HPA axis and ANS in CFS lay the groundwork for the possibility that many of the immunological abnormalities could be a result of the neuropsychological state or the accompanying neuroendocrine imbalance in CFS. One area of investigation not yet explored relates to the fact that glial cells, which comprise about 85% of all of the cells within the brain, are capable of producing a variety of cytokines and other immune mediators that can affect the neurons that they surround (Peterson et al. 1997, Chao et al. 1997). Thus, it is possible that a primary neuroimmunological disorder exists within the brains of CFS patients.

Of the more than 20 infectious agents that have been linked to fatigue syndromes during this century (Lloyd et al. 1997, Table 3), a large majority are neurotropic, i.e. microorganisms capable of infecting neural tissue (neurons or glia). Hypothetically, such agents could trigger on-going cellular dysfunction within the CNS giving rise to neuroendocrine and neuroimmunological imbalances as well as to many of the symptoms of CFS. This neuroimmunological model of CFS supports the observation that neurotropic viruses, such as influenza virus, EBV, human herpes-virus (HHV)-6, and Borna virus, as well as bacteria, such as *Borrelia burgdorferi* and *Coxiella burnetti*, can trigger the illness, and that a variety of risk factors, including gender, genetics, and severe

Table 3 Infectious diseases linked to fatigue syndromes*

Viruses	Bacteria	Parasites
Influenza (1892)†	Typhoid fever (1892)	Malaria (1869)
St. Louis encephalitis (1970)†	Alimentary bacteria (1911)	Schistosomiasis (1946)
Epstein-Barr virus (1948)†	Streptococcal infection (1922)	Toxoplasmosis (1988)†
Hepatitis A (1944)	*Brucella* (1934)†	
Yellow fever (1945)	Lyme disease (1990)†	
Varicella (1984)†	Q fever (1992)†	
Coxsackie B (1985)†		
Human herpesvirus-6 (1988)†		
Ross River virus (1990)		
Mumps virus (1990)†		
Retrovirus (1991)†		
Human herpesvirus-7 (1994)		
Borna virus (1996)†		

*Years in which infection was associated with fatigue syndromes are in parentheses (modified from Lloyd et al. (1997) with permission).

†Pathogens that have the capacity to invade, multiply, and elicit a pathological response within the brain.

Table 4 Viruses associated with multiple sclerosis

Virus	Year
Rabies virus	1946, 1964
Multiple sclerosis associated agent	1962
Herpes simplex virus	1964
Scrapie agent	1965
Parainfluenza virus 1	1972
Measles virus	1972
Simian virus 5	1978
Chimpanzee cytomegalovirus	1979
Coronavirus	1980
SMON-like virus	1982
Tick-borne encephalitis flavivirus	1982
HTLV-1	1986
LM7 (retrovirus)	1989, 1997
HSV-1	1989
MS1533 (retrovirus)	1994
HHV-6	1993, 1995

stress, can render the patient susceptible to development of CFS.

The number of viruses associated with CFS appears to have a parallel with another disease of presumed infectious etiology, multiple sclerosis (MS). MS, like CFS, has a female predominance, affecting women 1.5–2 times more often than men. The cause of MS is still unknown, although it is generally believed that environmental agents may be associated with this disorder. In theory, infection of genetically susceptible individuals may lead to abnormalities in host immune responses associated with disease pathogenesis.

Viruses have long been implicated in the etiology of MS (Johnson 1994). This is based on (1) epidemiological evidence of childhood exposure to infectious agents, increase in disease exacerbations with viral infection (Johnson 1994, Weinshenker 1996), (2) geographical association of disease susceptibility with evidence of MS clustering (Kurtzke et al. 1995, Haahr et al. 1997), (3) evidence that migration to and from high risk areas influences the likelihood of developing MS (Alter et al. 1996, Weinshenker 1996), (4) abnormal immune responses to different viruses (Neighbour et al. 1981, Jacobson et al. 1985), and (5) analogy with animal models and other human diseases in which viruses can cause diseases with long incubation periods, a relapsing remitting course, and demyelination (Johnson 1994, Weinshenker 1996). Many of these studies involve the demonstration of increased antibody titers to a particular virus, while some describe isolation of virus from MS material. However, no virus to date has been definitively associated with this disease. A partial list of viruses that have been reported over the past 50 years as associated with MS is given in Table 4. This list serves to reinforce the idea that while many viruses have been suggested to play a role in MS pathogenesis, as with CFS, none has been definitively proven to be the etiological agent in this disease. Alternatively, the information presented in Table 2 might imply that more than one virus may be associated with MS (as with CFS) which would be consistent with a disease of clinical variability involving multiple genetic loci and immune responses.

The virological parallels between MS and CFS are striking. In both disorders, retroviruses were considered as etiological agents (DeFreitas et al. 1991). More recently, reports have implicated the HHV-6. HHV-6 is a newly described (1986) betaherpesvirus which shares homology with cytomegalovirus (Yoshikawa et al. 1990), is considered the causative agent of exanthem subitum (roseola) in children (Yamanishi et al. 1988), and has been associated with CFS of adults (Patnaik et al. 1995). It is a ubiquitous herpesvirus with a seroprevalence rate in healthy adults of between 50 and 85% (Yoshikawa et al. 1990, Levine 1995). The first report suggesting that HHV-6 may be involved in MS appeared in 1993 (Sola et al. 1993) and demonstrated that anti-HHV-6 IgG antibody titers were significantly elevated in MS patients compared to normal blood donor controls. However, given the ubiquitous nature of this virus and the high seroprevalence rate in the general population, the association of increased IgG anti-HHV-6 serum antibody titers in MS was not very impressive. Moreover, an analysis of the presence of HHV-6 specific DNA sequences by the highly sensitive polymerase chain reaction (PCR) technique could only detect HHV-6 DNA in peripheral blood lymphocytes in one of 31 MS patients (Sola et al. 1993). Antibody titers to many viruses have been demonstrated previously to be increased in MS patients and are generally considered to reflect a more global defect in immune regulation than a specific marker of viral infection. Therefore, this early report was not very supportive in suggesting a role for HHV-6 in MS pathogenesis.

A more convincing study associating HHV-6 in MS was published in 1995 (Challoner et al. 1995) which utilized a technique known as representational difference analysis (RDA) to search for a pathogen in affected MS tissue. In RDA, successive rounds of subtractive hybridization and PCR amplification enriched for DNA sequences that were present in DNA from MS brain lesions, but were absent from normal brains. Importantly, this technique provides for an unbiased search for DNA sequences that are uniquely present in MS brain tissue relative to normal brain. The results from this search defined a 341 base pair fragment with virtual identity (99.4%) to the HHV-6 B variant. PCR analysis

utilizing this HHV-6 DNA sequence in MS and control brains demonstrated that HHV-6 could be detected in all samples, again confirming the high prevalence of this virus. However, immunohistochemical studies of MS lesions and normal brain material localized HHV-6 antigens in MS brains, in particular to the oligodendrocyte. The oligodendrocyte is the neural cell type that is involved in myelination of axons. Infection of oligodendrocytes in MS (a demyelinating disease) is an important observation, since the expression of HHV-6 antigen in this neural cell type suggests an involvement of HHV-6 in MS disease pathology.

More recently we had the opportunity to screen serum of MS patients for IgM and IgG antibodies to an early antigen of HHV-6 (p41/38) (Soldan et al. 1997). This same approach was used for the detection of IgM antibodies to HHV-6 p41/38 antigen in patients with CFS (Patnaik et al. 1995). Sera from a cohort of MS patients were screened in a blinded manner for IgM and IgG antibodies to the HHV-6 p41/38 affinity purified antigen in an ELISA assay and compared to sera from patients with other neurological diseases, patients with other inflammatory diseases and asymptomatic normal controls. There was no significant difference in the anti-HHV-6 IgG response to HHV-6 p41/38 early antigen among these groups, which was not unexpected as HHV-6 is ubiquitous and thought to be latent in approximately 90% of the adult population (Yoshikawa et al. 1990, Levine 1995). In contrast, there was a highly statistically significant difference in the anti-HHV-6 IgM response to HHV-6 p41/38 early antigen, particularly between the RRMS (relapsing remitting multiple sclerosis) group compared with normal controls ($P<0.0011$) (Soldan et al. 1997).

In support of these observations of an increase in IgM response to an early antigen of HHV-6 in remitting–relapsing MS, we have also demonstrated active HHV-6 in sera of MS patients by extraction and amplification of HHV-6 DNA using the nested PCR technique (Secchiero et al. 1995). Active virus has been demonstrated previously for HHV-6 by nested PCR in sera of children with exanthem subitum (roseola infantum) (Yamanishi et al. 1988). In contrast, active HHV-6 infection as measured by serum DNA could not be demonstrated in serum from normal adults (Secchiero et al. 1995). We have established such a system for the detection of HHV-6 DNA in serum of MS patients at a limit of detection of 0.045 femtograms of HHV-6 DNA. As has been reported for normal controls (Secchiero et al. 1995), no HHV-6 DNA was amplified from the serum of 47 non-MS patients tested. However, positive HHV-6 DNA signals were demonstrated in 30% (15/50) of MS patients ($P<0.0001$) (Soldan et al. 1997). Our ability to detect HHV-6 DNA in the serum of a subset of MS patients who were presumably infected with HHV-6 years ago indicates that the virus may have reactivated and could explain the increased IgM responses in some patients.

An infectious agent has been postulated as the cause for MS for over a century (Johnson 1994), and caution must be taken in the interpretation of studies suggesting virus associations in this disorder. Increased antibody responses to a variety of viruses have been reported in this disease. It is still unclear whether this represents disease-specific immune responses or is an epiphenomenon of a more generalized immune abnormality. With the advent of newer molecular tools to search for viral genes and their products, surveys of MS tissue for virus-specific genetic sequences have begun. It remains to be determined whether a unique MS-associated virus will be demonstrated. In this regard a report in 1997 characterized a potentially novel human retrovirus with partial homology to endogenous human retroviral sequences that could be detected by nested PCR in non-cellular RNA from a subset of MS patients, serum and CSF (Perron et al. 1997). However, a more likely scenario suggests that a ubiquitous virus or viruses may be associated with MS in which infection of a genetically susceptible individual may lead to abnormalities in immune regulation that result in the destruction of essential neuroglial elements that produces clinical disease.

Further studies are needed to clarify these issues in MS, and their relevance to CFS is obvious. It is important to note that historically MS was considered to be a depressive rather than a neurological illness, which makes the approach to understanding the etiology and pathogenesis quite relevant to CFS. Additionally, the history of HHV-6 studies in CFS may well be relevant to MS, with the final story not yet told. While HHV-6 antibody titers have been noted to be elevated in CFS and HHV-6 infected cells were reported in one northern Nevada cluster associated with CFS (Buchwald et al. 1992, Patnaik et al. 1995), a number of other viral antibodies have also been reported in both case series and in the northern Nevada cluster (Holmes et al. 1987). We approached the role of HHV-6 as an important agent in maintaining CFS symptoms with a clinical trial using dialyzable lymphocyte extract (DLE) with documented activity against HHV-6 (Ablashi et al. 1997, Levine et al. 1997). In one well-studied patient (Ablashi et al. 1997), the DLE appeared to be extremely effective, with a disappearance of the large apparently HHV-6 infected cells from the circulation and a dramatic decrease in HHV-6 antibody titer from the circulation. However, there was no effect on the clinical course of CFS in this patient.

Conclusions

While our understanding of CFS continues to evolve, its relevance to the field of neuroepidemiology and infections is readily apparent. First, the potential role of infection is important for historical reasons because of the apparent association of CFS with some outbreaks of EN (Poskanzer et al. 1957, Levine et al. 1992, 1997) and the linkage of EN with significant neurological symptoms (Briggs and Levine 1994). The number of CFS cases in each outbreak is variable, and the diagnosis of CFS *per se* could not be made before the case definition was developed in 1988. In two outbreaks we have investigated, however, it is clear that the criteria for CFS were met, including the careful medical evaluation to rule out other disorders, and the medical follow-up continuing for 10 years after the initial cluster report. Second, a majority of the symptoms in sporadic cases of CFS, which are more prominent in the US than are cluster cases, commonly precipitate neurological assessments. Such symptoms include severe headache, cognitive abnormalities, sleep disorders, and paresthesias.

Third, mounting evidence suggests that neurotropic pathogens may be involved and that in a large subgroup of patients CFS may ultimately be viewed as a neuroimmunological disorder triggered in susceptible hosts by these infectious agents.

There are several critical issues that hamper epidemiological studies of CFS. First, there is no diagnostic or confirmatory test for CFS, and although considerable progress is being made in unravelling the immunological and neuroendocrine abnormalities in CFS, these abnormalities are inconsistent and generally modest, with considerable overlap between CFS patients and control groups.

The absence of a diagnostic marker has further complicated the difficulties with case definition. CDC, as the agency responsible for following disease patterns in the US, has initiated the process by attempting a series of case definitions (Holmes et al. 1988, Fukuda et al. 1994) which, for practical and economic reasons, have been replaced in some CDC studies by "CFS-like" (Shefer et al. 1997), since medical evaluations are not included. CFS and idiopathic chronic fatigue as defined by Fukuda et al. (1994) may well share the same pathogenesis and CDC-defined CFS is clearly "the tip of the iceberg".

Any conclusions regarding the epidemiology of CFS are likely to change in the coming years, but certain observations appear reasonable at the present time. First, CFS is a heterogeneous disorder and only a proportion of cases, albeit a significant one (Salit 1997), are associated with infection. Second, the precipitating infectious agents are diverse, including *giardia*, *borrelia* and a wide variety of viruses, many of them neurotropic. Third, the CNS plays an important role in pathogenesis, with abnormalities of the HPA in most cases. The possibility of cytokine-mediated immunopathology as one of several neurological dysregulations requires further study, particularly in view of animal studies of immunologically mediated fatigue (Chao et al. 1992, Sheng et al. 1996). Finally, it appears that stress often plays an important role in pathogenesis, and the control of stress through cognitive behavioral therapy may be of value in limiting the impact of the illness on the patient. The prognosis for any individual is unpredictable, but recovery can be complete, rehabilitation can be effective (Furst et al. 1995), and early treatment of symptoms by an experienced physician with current reliable knowledge of CFS is extremely important.

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